



TITLE:

# EXPERIMENTAL AND CLINICAL STUDIES ON PROFOUND HYPOTHERMIA

AUTHOR(S):

KUWANA, KAZUO

---

CITATION:

KUWANA, KAZUO. EXPERIMENTAL AND CLINICAL STUDIES ON PROFOUND  
HYPOTHERMIA. 日本外科宝函 1962, 31(2): 158-180

ISSUE DATE:

1962-03-01

URL:

<http://hdl.handle.net/2433/205434>

RIGHT:

# EXPERIMENTAL AND CLINICAL STUDIES ON PROFOUND HYPOTHERMIA

by

KAZUO KUWANA

From the 2nd Surgical Division, Kyoto University Medical School  
(Director : Prof. Dr. YASUMASA AOYAGI)

Received for publication Jan. 9, 1962

## A. PREVENTION OF PULMONARY COMPLICATION IN PROFOUND HYPOTHERMIA

### I. INTRODUCTION

The recent development of cardiac surgery mostly depends upon the artificial heart-lung apparatus and hypothermia. However, artificial heart-lung apparatus has many drawbacks such as requirement of a large amount of heparinized blood, development of the cerebral or coronary air embolism, difficult management of the apparatus. On the other hand, hypothermia which makes circulatory occlusion possible for an adequate time to perform intracardiac surgery by the reduced metabolism is advantageous in sparing of cost, rather easy management and complete dry field for intracardiac surgery.

However, it has been pointed out that hypothermia was disadvantageous in development of ventricular fibrillation and pulmonary edema which were easily produced by inadequate management of anesthesia.

The lower the body temperature, the longer will be the safety time limit for circulatory occlusion, but the higher is the incidence of cardiopulmonary complications. One of the most serious complications under hypothermia is ventricular fibrillation for which prevention has been investigated by many authors.

SAITO has stated that the electric threshold value for ventricular fibrillation at 18° to 19°C of rectal temperature was elevated by administration of essential fatty acids (E. F. A.). He also described that administration of E. F. A. prior to the hypothermia was effective in the prevention of ventricular fibrillation. In facts, the dogs to whom right ventriculotomy was performed under hypothermia were successfully resuscitated and most of them survived over 2 weeks postoperatively.

Our collaborators, KOBAYASHI and NAGASE have reported that water intoxication or pulmonary edema was easily developed in the animals in E. F. A. deficiency because of the increased vascular permeability.

TOMIOKA has demonstrated that the abnormal increases in hematocrit and blood viscosity produced by increased vascular permeability under hypothermia was effectively prevented by administration of E. F. A.. He also stated that since the peripheral vascular hemodynamics were maintained within normal limits because of the above reason and the period of cooling and rewarming time in the E. F. A. group was shortened than that in

the controls.

It has been stated that in order to prevent pulmonary edema, it was necessary to supply enough oxygen by intermittent positive artificial respiration. It is suggested that pulmonary complications should be prevented by administration of E. F. A., because of the above reason. In facts, the expected results were obtained in the present study. However, in an ambient temperature of 10°C in winter, most dogs even in E. F. A. group died of pulmonary edema after cardiac surgery under hypothermia. It is the purpose of the present study to investigate how to prevent pulmonary edema even in severe cold atmosphere.

## II. EXPERIMENTAL METHODS AND MATERIALS

### 1) Animals

Infant mongrel dogs (under one year old) weighing 6 to 12kg were used, because, most adult dogs have filarias in the right ventricle who eventually become pulmonary emboli after cardiac surgery. The author selected successfully the dogs adequate to the experiments by the remark of the growth of teeth.

### 2) Administration of E. F. A.

Linoleic acid (9-12-octadecadienoic acid), linolenic acid (9-12-15-octadecatrienoic acid) and arachidonic acid (5-8-11-14-eicosatetraenoic acid) are known as E. F. A. today, among of which arachidonic acid has the specific nutritional effect of E. F. A. in vivo. This is synthesized from linoleic acid with the aid of Vitamine B6. Therefore, linoleic acid has the same effect as arachidonic acid. In order to correct deficient state of E. F. A., sesame oil or soya lecithin containing a sufficient amount of linoleic acid and linolenic acid was administered to the dogs in E. F. A. deficiency. Usually, soya lecithin in a dose of 5g was administered by mouth or 20% sesame oil emulsion produced in our laboratory in a dose of 25 cc was infused intravenously daily for one week prior to the experiments.

### 3) Other premedications

a) SAITO has stated that dimethylaminoethanol (D. A. E.) or precursor of acetylcholine had an antifibrillatory effect, in consequence, the electrical threshold value for ventricular fibrillation in E. F. A. plus D. A. E. group was higher than in the E. F. A. group alone. In the present study, D. A. E. was also given to the dogs. Eason (acidic tartaric soda) or recrein (paraaminosoda) in a dose of 10mg was given by mouth daily for one week prior to the experiments as D. A. E.. There were no difference in effect between eason and recrein.

b) Vitamine E (ephynal-dl- $\alpha$ -tocopherol) in a dose of 200mg was administered by mouth daily for one week prior to the experiments.

4) Pyrethiazine (HCl-prométhazine) in a dose of 0.5mg per kg was subcutaneously injected postoperatively.

### 5) Experimental methods

The present study was performed by the following method as SAITO has applied.

(i) Atropine was injected as premedication. Endo-tracheal tube was inserted with the aid of the intravenous administration of thiopental. Anesthesia was maintained deep

enough to control shivering by the closed system inhaling ether and oxygen mixture.

(ii) The dogs were cooled by immersion method.

(iii) Neostigmine in a dose of 0.25mg was subcutaneously injected at 25°C rectal temperature.

(iv) Cooling was discontinued at 24° to 19°C rectal temperature. The chest was entered through the left 5th intercostal space. After opening the pericardium, heparin (in a dose of 1.5mg per kg) was administered into the left ventricle.

(v) Circulation was occluded after the heart muscle was well oxygenated by pressing the thoracic aorta.

(vi) YOUNG's solution without additional neostigmine was employed as cardioplegic. The artificial cardiac arrest was produced by the rapid coronary perfusion of this solution. Immediately thereafter, right ventriculotomy was done.

(vii) Before release of occlusion, YOUNG's solution was washed out from the heart muscle by the rapid coronary perfusion of physiologic saline solution.

(viii) After release of occlusion, cardiac massage was done under pressing the thoracic aorta. In the dogs in E. F. A. group and E. F. A. plus D. A. E. group, normal cardiac beat was obtained within 1 or 2 minutes after release of occlusion. Intrathoracic rewarming was done carefully observing the cardiac beat. The dogs to whom ventriculotomy was done at above 22°C rectal temperature were successfully resuscitated, being converted to the normal cardiac beat by cardiac massage alone without pressing the thoracic aorta.

(ix) Pressure to the thoracic aorta was released at about 22°C rectal temperature.

(x) Immersion rewarming was done at above 25°C rectal temperature.

(xi) The chest was closed at above 30°C rectal temperature.

(xii) Prométhazine in a dose of 0.5mg per kg was injected subcutaneously 2 times separately after rewarming.

(xiii) Heparin was neutralized by the intravenous injection of protamine-sulfate in a dose of 1.5 times volume as much as heparin, protamine-sulfate being diluted with 20 cc of physiologic saline.

### III. EXPERIMENTAL RESULTS AND DISCUSSION

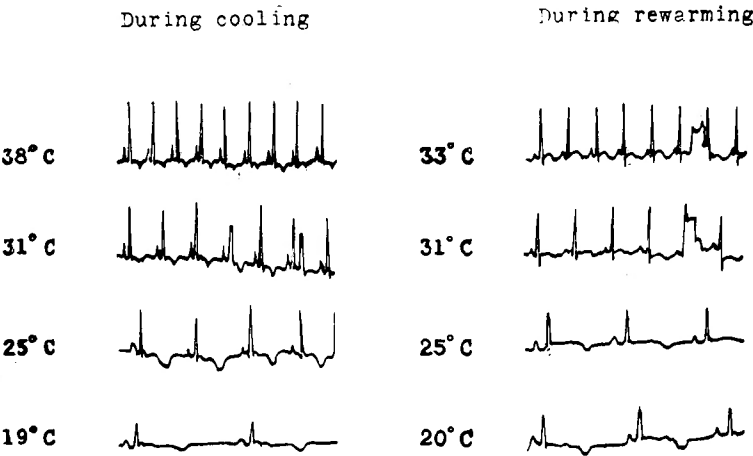
As mentioned above, the author demonstrated that the dogs suffered from ventriculotomy under hypothermia could be successfully resuscitated at above an ambient temperature of 10°C (Table 1). However, in severe cold atmosphere (under an ambient temperature of 10°C) even the dogs in E. F. A. group or E. F. A. plus D. A. E. group died of pulmonary edema postoperatively. As is given in Fig. 1, dogs died of pulmonary edema within 5 to 12 hours after resuscitation, even though administration of fluid was not done. In these cases, cortison was not effective in prevention of pulmonary edema. Pulmonary edema was suspected by the bloody bubble in endotracheal tube, pulmonary hepatization and microscopic picture. It is suggested that pulmonary edema was produced by pulmonary congestion due to cardiac failure during the period of rewarming to 25°C rectal temperature after release of occlusion. In this mind, the author attempted to prevent pulmonary congestion by the increase in coronary blood flow by application of

**Table 1** Long Term Survival Experiment (Over 2 Weeks)  
Right Ventriculotomy was Performed

Dog No.	Wt. of dog	The lowest rectal temperature	Occlusion time	V. F.	P. C.	Heart massage	Result	Cardioplegica
	kg	°C	min.			min.		
1(S)	6.2	18.2	20	no	no	<3	survived	Young's Solution
7(S)	8.5	18.0	20	no	no	<3	survived	"
10(S)	9.5	18.0	21	no	no	<3	survived	"
12(L)	7.0	18.5	31	no	no	<3	survived	"
14(L)	9.2	19.0	20	yes	no	23	survived	Potassium citrate
19(L,D)	6.7	19.0	24	no	no	<3	died (Pyothorax)	
20(L,D)	10.0	19.0	26	no	no	<3	survived	Young's Solution

S : 20% Sesame oil emulsion      L : Soya lecithin      D : Dimethyleminoethanol  
V. F. : Ventricular fibrillation      P. C. : Pulmonary complication

**Fig. 1** Electrocardiogram of the dog in E. F. A. plus D. A. E. group who died of pulmonary edema postoperatively after uneventful resuscitation under hypothermia (Lead II).



Note : This is quite equal to the long survival dogs.

pressure to the thoracic aorta for a long period of time.

However, this procedure produced pulmonary edema easily in shorter time and the degree of pulmonary edema in microscopic findings became more severe. As is given in Fig. 2, microscopic findings in the lung of the dog died of pulmonary edema under hypothermia revealed the remarkable transudation into the alveolar space and severe inflammatory changes.

These experimental results clearly demonstrate that pulmonary edema is produced by hypothermia and more easily by high pulmonary arterial pressure caused by application of pressure to the thoracic aorta.

It has been observed that the subcutaneous blood vessels contracted transiently and then enlarged by cold stress. When the individuals were exposed to cold for a long time, the blood pooling in capillaries and transudation or edematous changes in the tissues were observed.

It is well known that tocopherol has the effect to prevent frost bite. This fact is attributed to the preventive effect of increase in permeability of capillaries at low body temperature. Moreover, tocopherol has the effect in prevention of myocardial degeneration. Because of these reasons, the author administered not only E. F. A. and D. A. E., but also tocopherol as premedication in order to prevent pulmonary edema. The dogs to whom Vit. E, E. F. A. and D. A. E. were administered prior to the experiments were suffered from ventriculotomy under cardiac arrest for 20 minutes as our usual procedure, and after resuscitation, prométhazine that possesses the antiacetylcholine-like effect and the effect to prevent increase in vascular permeability was administered.

As is given in Table 2, all dogs in this group were uneventfully resuscitated without pulmonary edema even in severe cold atmosphere (in an ambient temperature of 5° to 10°C). On the other hand, 5 out of 7 dogs in the controls died of pulmonary edema. The dogs who were given Vit. E, E. F. A. and D. A. E. survived after they suffered from ventriculotomy under cardiac arrest even for 50 minutes (Table 3). From these experiments, it was also clarified that the cardiac arrest even for 50 minutes under hypothermia below 22°C rectal temperature was safe (Fig. 3). To be noticed in the present study, pulmonary edema was prevented more effectively by administration of both E. F.

**Table 2** Long Term Survival Experiment in Winter (Over 2 Weeks)  
Right Ventriculotomy was Performed

Dog No.	Wt. of dog	Ambient temperature	The lowest rectal temperature	Occlusion time	V. F.	P. C.	Result	Postoperative administration
	kg	°C	°C	min.				
Vitamin E free group (Controls)								
20(L,D.)	10.2	5.3	19.0	26	no	no	survived	Cortison
21(L,D.)	8.2	13.0	19.0	30	no	no	survived	
22(L,D.)	9.5	6.4	19.5	21	no	yes	died	
23(L,D.)	8.5	10.0	18.0	30	no	yes	died	
24(L,D.)	6.7	6.5	18.0	30	no	yes	died	
25(L,D.)	5.8	8.0	19.0	21	no	yes	died	
26(L,D.)	5.7	5.0	19.0	22	no	yes	died	
Prométhazine } + }group Vitamin E }								
27(L,D,E)	7.6	4.5	19.0	20	no	no	survived	Prométhazine
28(L,D,E)	5.8	10.0	19.5	20	no	no	survived	//
29(L,D,E)	6.1	8.2	18.3	20	yes	no	survived	// (A)

L : Soya lecithin    D : Dimethylaminoethanol    E : Vitamin E

A : Ventricular fibrillation occurred at the change of position after release of occlusion.

V. F. : Ventricular fibrillation    P. C. : Pulmonary complication

**Table 3** Long Term Survival Experiment in Winter (Over 2 Weeks)  
Right Ventriculotomy was Performed

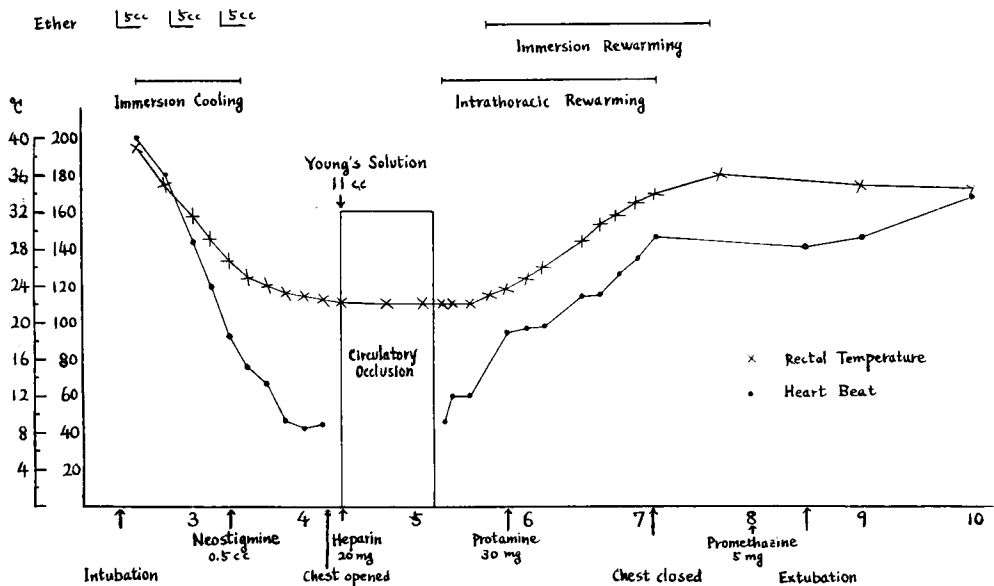
Dog No.	Wt. of dog	The lowest rectal temperature	Occlusion time	Time to normal heart beat	V. F.	P. C.	Result	Postoperative administration
	kg	°C	min.	sec.				
31(L,D,E)	8.5	18.3	50	130	no	no	survived	Prométhazine
32(L,D,E)	7.5	18.0	50	22	no	no	survived	"
33(L,D,E)	7.5	19.5	50	12	yes	no	survived	" (A)
34(L,D,E)	6.8	21.0	50	130	no	no	survived	"
35(L,D,E)	8.0	22.0	50	45	no	no	survived	"

L : Soya lecithin D : Dimethylaminoethanol E : Vitamin E

A. Ventricular fibrillation which occurred at the change of position during rewarming was converted to the normal heart beat easily by electric shock.

V. F. : Ventricular fibrillation P. C. : Pulmonary complication

**Fig. 3** Chart of anesthesia of the dog whose circulation was occluded for 50 minutes at 22°C rectal temperature.



A. and Vit. E than E. F. A. or Vit. E alone.

#### IV. CONCLUSION

In the present study, it was investigated how to prevent pulmonary edema under hypothermia. The following results were obtained.

1) To prevent pulmonary edema under hypothermia, it is necessary to administer a sufficient amount of E. F. A. and Vit. E for about one week prior to the operation and prométhazine in a dose of 0.5mg per kg subcutaneously after resuscitation.

2) According to SAITO, E. F. A. is much effective also in prevention of cardiac complications under hypothermia. In consequence, in order to prevent cardio-pulmonary complications under hypothermia, administration of E. F. A. and Vit. E prior to the operation and prométhazine after resuscitation is necessary.

3) By doing so, the animals survive after they suffered from ventriculotomy under cardiac arrest even for 50 minutes under hypothermia below 22°C rectal temperature.

## B. MICROSCOPIC STUDIES

### I. INTRODUCTION

In the previous study, it was investigated how to prevent pulmonary complications which were often encountered under hypothermia in order to establish a new technique of hypothermia. With the help of this new technique of hypothermia, the animals survived after they suffered from ventriculotomy under hypothermia at 18° to 22°C rectal temperature. Then the next question arises if these survivals present the abnormal histological changes in their vital organs.

In the present study, survivals after ventriculotomy under hypothermia were sacrificed at various days after experiments in order to investigate the microscopic changes in vital organs. Furthermore, the microscopic changes in the organs of the dogs whose circulation was occluded for 20 and 50 minutes were compared. From these results, it was attempted to discuss the safe time limits of circulatory occlusion at various rectal temperature.

### II. METHODS AND MATERIALS

#### 1) Animals

Under one year old mongrel dogs weighing 6 to 10 kg were used.

#### 2) Technique of hypothermia and surgical operation

These were essentially the same as in the previous study. The survivals after right ventriculotomy under cardiac arrest for 20 and 50 minutes with the help of hypothermia at 22°C rectal temperature were sacrificed at various days after experiments.

#### 3) Histological specimens

The both femoral arteries and abdominal aorta were cut to sacrifice the dog. The histological specimens were obtained from the definite portion of organs and were dyed by hematoxyline-eosine, Sudan III and NISSLE's dyeing.

The dog No. 9 in Table 4 reveals the microscopic changes of the dog with myocardial insufficiency whose descending branches of the left coronary arteries were ligated in normothermia about 1 month prior to the operation. He suffered from ventriculotomy under cardiac arrest for 20 minutes with the help of hypothermia and was sacrificed 30 days after operation. It was observed that the pericardium was adherent to the heart and the part of the myocardium maintained by the ligated coronary artery was very thin.

### III. RESULTS AND DISCUSSION

#### 1) Central nervous system



**Table 4** Histological Findings of Organs at Various Days after Experiment

After experiment		Immediately after	5 days after	10 days after	20 days after	30 days after					
Organ	Histological findings	Occlusion time (min.)									
		20	50	20	50	20	50	20	50		
Central nervous system (Purkinje's cell in cerebellum)	Shrinking and Homogenization of cell	—	—	±	—	±	—	—	—	—	
	Change of nucleus	±	±	±	±	±	±	±	±	±	
Lung	Atelectasis	—	—	—	+	—	—	±	±	—	—
	Thickening of pleura	—	—	±	—	—	+	—	+	+	+
	Bronchitis	±	±	±	—	±	—	—	—	—	—
Heart	Myodegeneration	±	±	+	+	+	+	+	+	±	±
	Calcification	—	—	—	±	+	+	+	+	+	+
Liver	Degeneration of hepatic cell	—	—	+	±	+	+	±	±	±	±
	Cell infiltration	—	—	+	±	±	±	+	+	+	+
Spleen	Cell infiltration	±	±	±	+	±	—	±	—	±	—
	Hemosiderosis	—	—	—	—	—	—	±	—	±	—
Kidney	Degeneration of tubular cell	—	—	—	—	±	±	—	—	±	—
	Cell infiltration	—	—	—	—	—	—	—	—	+	—

No. 9: The dog with myocardial insufficiency

No hemorrhage and necrosis in the central nervous system were observed in dogs whose circulation was occluded for 20 and 50 minutes.

It has been stated that the PURKINJE's cells in cerebellum were sensible to hypoxia. In the present study, very slight deviation of nucleus and nucleolus, shrinking and homogenization in a part of the PURKINJE's cells were observed (Figs. 4 and 5). To summarize, the significant organic changes in the central nervous system were not observed.

## 2) Heart

There were not significant differences. The histological changes of myocardium in dogs whose circulation was occluded for 20 and 50 minutes were not significant.

Calcification of myocardium were observed 10 days after operation in both group. This changes were dominant in the dog with myocardial insufficiency (Fig. 11). In a part of myocardium, granular protoplasm, swelling of myocardial fibers (myodegeneration) were observed (Figs. 10 and 12). Day after day, these degenerations changed to calcification (Fig. 13). However, electrocardiogram in these cases showed no pattern of myocardial insufficiency.

It is obvious that cardiotomy, circulatory occlusion and hypothermia itself result in these microscopic changes in the myocardium. Moreover, it may be thought that administration of cardioplegica is one of the factors that produced the histologic changes in the myocardium.

On the other hand, in the present study Vit. E which prevents myocardial

degeneration was administered preoperatively. In consequence, microscopic changes in myocardium was so slight as to be able to apply YOUNG's solution clinically as cardioplegic under hypothermia.

### 3) Lung

Since pulmonary complications were prevented by the above procedures, pulmonary edema was not detected microscopically in all cases.

However, slight catarrhal bronchitis and inflammatory changes of alveoli around bronchus were observed for several days after operation (Fig. 6. and 9). These changes became gradually slighter day after day and disappeared after 10 days postoperatively. Since the lung expanded sufficiently postoperatively, pulmonary emphysema or atelectasis was not observed (Fig. 8). The pleura tends to get thicker day after day (Fig. 7).

The microscopic changes in the lung were quite equal to the dogs whose circulation was occluded for 20 and 50 minutes.

### 4) Liver

The microscopic changes in the liver also were quite equal to the dogs whose circulation was occluded for 20 and 50 minutes.

The hepatic cells in lobules were arranged architecturally in slight atypical fashion and the slight vacuolar degeneration in the hepatic cells were observed within 10 days after operation (Figs. 14 and 15). However, these changes disappeared 20 days after operation.

On the other hand, cell infiltration in the area around the GLISSON's capsule was observed even after 20 days after operation (Fig. 16).

To summarize, the microscopic changes in the liver were little for life and gradually converted to the normal picture postoperatively. It is thought that the changes in the liver were produced by ether which is toxic to the liver, or rather than hypothermia itself.

### 5) Kidney

The abnormal microscopic changes in the kidney were not observed except the dog with myocardial insufficiency who was sacrificed 30 days after ventriculotomy under cardiac arrest for 20 minutes. The local small cell infiltration in the cortex of the kidney and the granulation tissue in the medulla of the kidney were observed in the dog with myocardial insufficiency (Figs. 17 and 18). Its etiology is unknown.

### 6) Spleen

The very slight inflammatory changes alone were observed in the spleen within 10 days after operation (Fig. 20).

As mentioned above, if the dogs suffered from ventriculotomy under cardiac arrest for 20 to 50 minutes with the help of our new technique of hypothermia at 22°C rectal temperature, fatal defects in the microscopic changes of various vital organs were not observed. The changes in the liver are thought to be resulted by anesthetic gas, ether, or rather than hypothermia.

From these reasons, hypothermia might be safely employed clinically. Furthermore, liver damage due to ether may be prevented by extensive pre- and postoperative medical treatment and by doing so, hypothermia might be employed more safely.

#### IV. CONCLUSION

The dogs suffered from ventriculotomy under cardiac arrest for 20 and 50 minutes with the help of our new technique of hypothermia at 22°C rectal temperature in order to investigate the microscopic changes of vital organs caused by hypothermia. The microscopic studies in the survivals who were sacrificed at various days after experiments lead to the following results.

1) Even if circulation was occluded for 20 to 50 minutes at 22°C rectal temperature, fatal microscopic changes were not observed.

2) The changes in the liver are thought to be produced by ether, or rather than hypothermia. In consequence, this seems to be prevented by extensive pre- and post-operative medical treatment for the liver.

3) YOUNG's solution might be safely employed clinically as cardioplegica.

#### C. CLINICAL STUDIES

##### I. INTRODUCTION

In the previous study, it was investigated how to prevent the pulmonary complications under hypothermia. And from our collaborators' and the author's results, the new unique hypothermia was introduced. In the present study, it was attempted to investigate if the clinical application of this new hypothermia are adequate.

As is well known, hypothermia has been applied not only to the cardiac surgery under direct vision, but also to the intracranial operation.

Furthermore, the pediatric surgery has also been frequently performed with the help of hypothermia, which is much effective to the prevention of hyperpyrexia (heat retention), tachycardia and water and electrolytes unbalance during and after operation in children. Representatives out of the cases to which our new hypothermia was applied in our clinic were discussed.

##### II. CLINICAL APPLICATION OF HYPOTHERMIA

###### 1) A case of arterio-venous malformation

The following case clarified that the preoperative administration of E. F. A. and Vit. E was effective to the safety in the course of hypothermia.

The male, 32 years old patient admitted to the 1st surgical division in our medical school under the diagnosis of arterio-venous malformation in the left parietal region.

Mild hypothermia was applied to him to clip the afferent arteries under craniotomy. However, since severe ventricular arrhythmia, cyanosis, and unstable blood pressure have developed at about 29°C rectal temperature, the surgery was cancelled (Fig. 21).

Thereafter, he was given soya lecithin in a dose of 15 to 20 g by mouth daily for one week prior to the next operation. Then, it was attempted to clip the afferent arteries to angioma under craniotomy in our routine hypothermia at 29°C rectal temperature. The blood pressure was maintained within normal limits and arrhythmia was not enco-

Fig. 21 Diagnosis : Arteriovenous Malformation of Left-Parietal Region  
(Operation was Cancelled) Age : 32 Years Old Sex : Male  
The Lowest Rectal Temperature : 29.0°C.

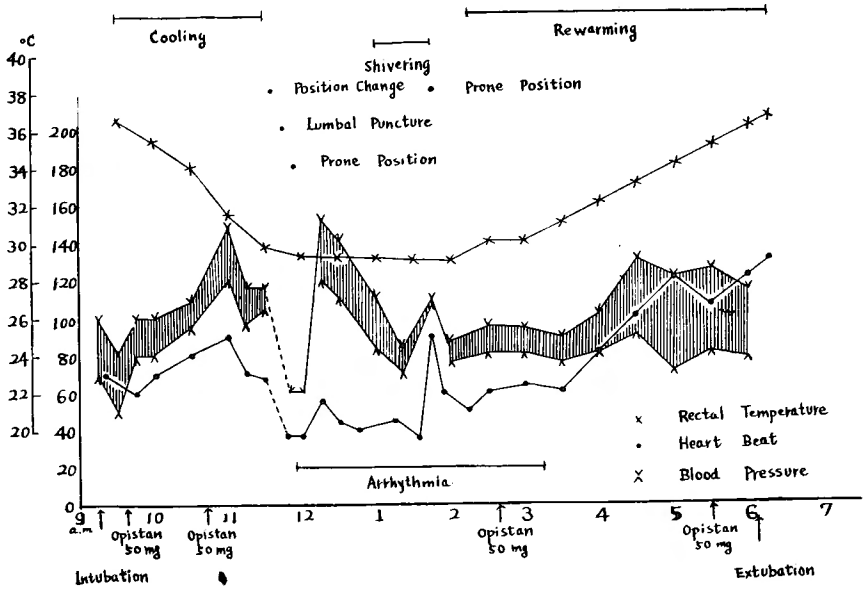
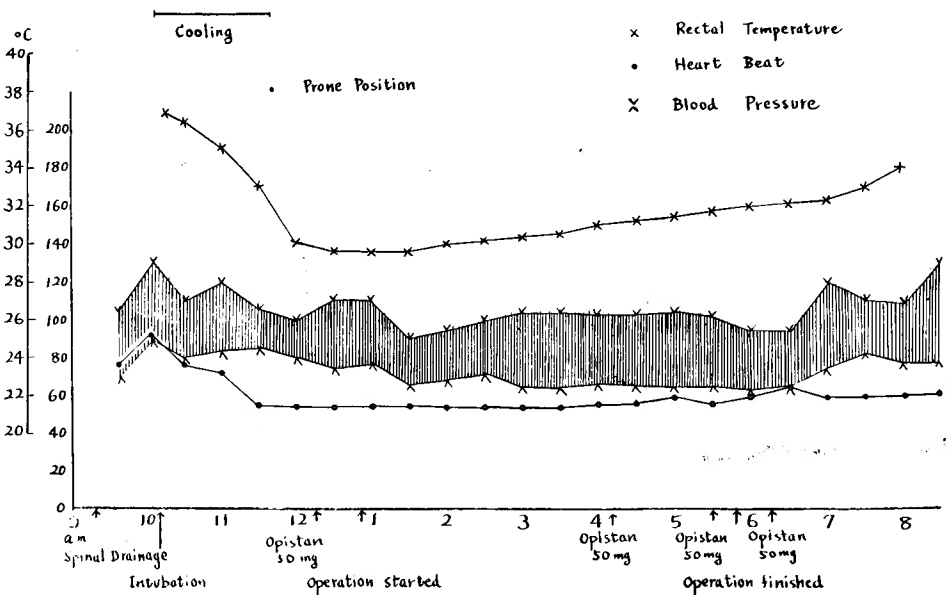


Fig. 22 Diagnosis : Arteriovenous Malformation of Left-Parietal Region  
Age : 32 Years Old Sex : Male  
The Lowest Rectal Temperature : 22.3°C.



untered during the second attempt of hypothermia and the clipping was successfully performed. The postoperative course was uneventful (Fig. 22).

This experience clarified that the preoperative administration of E. F. A. was effective to maintain the myocardial function normal during hypothermia.

As SAITO has stated, deficit of E. F. A. causes the dissociation of oxidative phosphorylation that disturbs the synthesis of ATP, energetic source, to make the muscle contract. Consequently, deficit of E. F. A. depress the myocardial function. In facts, active heart muscle contains far much more amount of E. F. A. than the other muscles. On this point of view, preoperative administration of E. F. A. might be the adequate treatment to maintain the myocardial function.

In craniotomy, there are many cases in which hypothermia must be continued for a long time in order to prevent postoperative elevation of intracranial pressure and cerebral edema. This prolonged hypothermia is disadvantageous in the presence of hemorrhagic diathesis caused by the decrease in fibrinogen and platelets due to hypothermia. Furthermore, the methods of prevention of pulmonary edema described in part A and C are not sufficient in this prolonged hypothermia. Further investigations for prevention of pulmonary edema and bleeding tendency during prolonged hypothermia are expected.

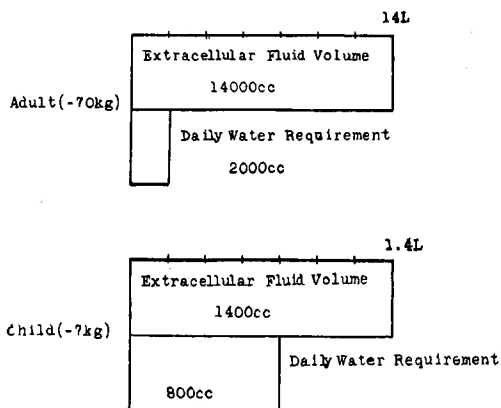
## 2) 2 Cases in pediatric surgery

In general, water metabolism and electrolytes balance in children is an especially important factor.

The rate of water metabolism in infants and children reaches its peak at about 2 years of age and thereafter it declines gradually year after year. Consequently, it is suggested that water must be given 120 cc per kg of body weight to infant under 2 years of age, 90 cc per kg 3 to 4 years of age and 60 cc per kg about 5 years of age. The ratio of daily water intake to extracellular fluid volume is about one half in children, on the other hand, one seventh in the adults (Fig. 23). Therefore, the very rapid turnover of fluid, involving consistently large intake as well as excretion of water, sets the stage for dangerous and sudden departures either on the side of excessive intake and overhydration or on excessive loss and dehydration. On this point of view, administration of an adequate volume of water must be done carefully.

As to electrolytes, chloride concentration in plasma is 110 mEq per liter in infants and 103 mEq per liter in adults. On the contrary, bicarbonate concentration in plasma is 20 mEq per liter in infants and 27 mEq per liter in adults. Thus, chloride and bicarbonate concentration in plasma between infants and adults have a contradictory relation. Furthermore, the buffering mechanism in young infants is not fully effective in infants, giving a tendency towards

Fig. 23 Relation between daily water requirement and extracellular fluid in child and adult.



acidosis.

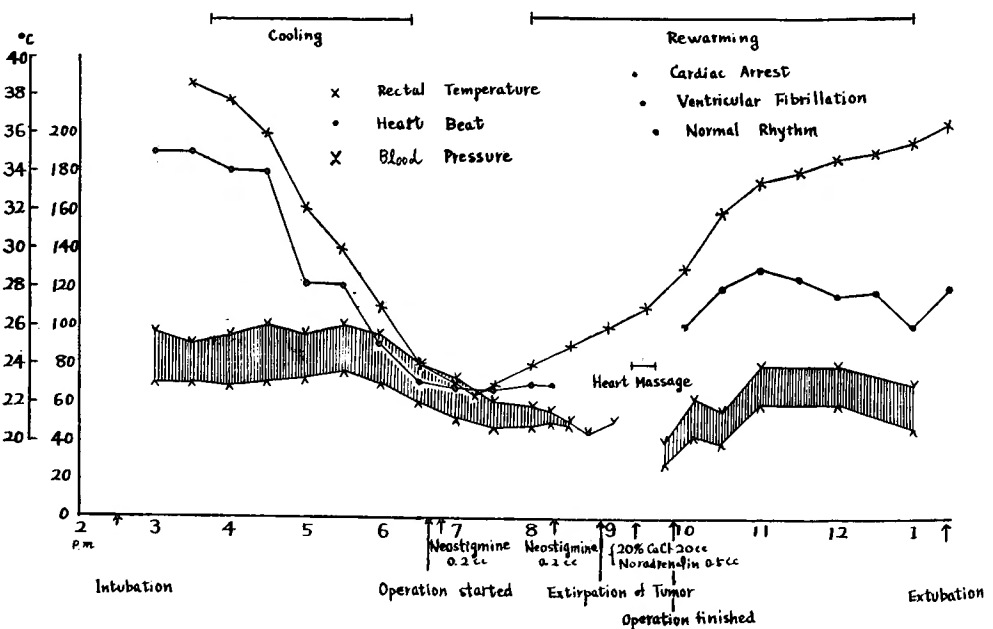
Therefore, in order to treat the dehydration in children, it is necessary to administer not only fluid, but also proper electrolytes. In our clinic, pediatric surgery is performed after fluid balance and blood volume were adequately controlled as preoperative care, observing the grade of dry skin, urine volume, body temperature, grade of cave of fontanel, grade of anemia and circulating blood volume. The author will discuss the representative 2 cases, which offered to us much suggestive experiences in pediatric surgery under hypothermia.

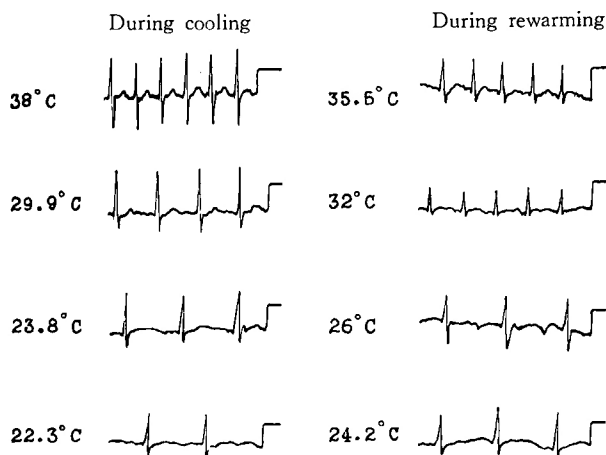
The patient is one year and 8 months old, having WILM's tumor. Not only fluid and electrolytes balance were controlled, but also soya lecithin in a dose of 5 g and Vit. E by mouth daily for 5 days were given preoperatively.

WILM's tumor weighing 1.6 kg was removed from her weighing 9 kg with the help of hypothermia at 22.3°C rectal temperature (Fig. 28). Duration of operation was 2 and a half hours. Blood loss was 1080 cc, particularly when the tumor was dissected free from the diaphragm and liver, bleeding was great (Figs. 26 and 27).

Immediately after the extirpation of the tumor which was ended by the dissection from the diaphragm and liver, sudden cardiac arrest occurred. Emergency left thoracotomy was performed to massage the heart, blood being rapidly transfused. Transient ventricular fibrillation occurred when cardiac massage was started after 5 mg of noradrenalin was injected in the left ventricle. This ventricular fibrillation was soon converted to normal cardiac beat only by cardiac massage and her postoperative course was uneventful (Figs. 24 and 25).

Fig. 24 Chart of Hypothermic Anesthesia Diagnosis: Right WILM's Tumor  
Age: 1 Year and 8 Months Old Sex: Female  
The Lowest Rectal Temperature: 22.3°C.



**Fig. 25** Electrocardiogram during hypothermia (Lead II).

Preoperative care to this patient was carefully done as mentioned above. Besides, anesthesia was carefully managed and minute to minute control of fluid and blood replacements during operation was performed by observing the measurement of blood loss and urinary volume drained from the bladder catheter. To be noticed at this time, rapid fluid transfusion tends to produce the pulmonary edema in children. Therefore, rapid fluid transfusion in a dose of 50 to 100 cc at a time which is often performed in the adults must be avoided in children as possible. In consequence, as a rule, intravenous continuous drip infusion of 5% glucose solution must be applied during and after operation.

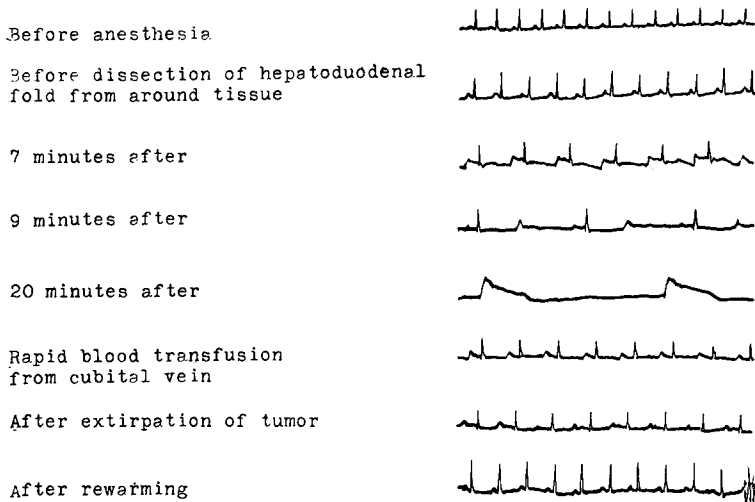
In this case, too, the above procedures were done carefully. Then, why did the cardiac arrest occur at the time when the tumor was removed? It is suggested that the large bleeding at the time of extirpation of the tumor might be the cause of cardiac arrest.

Our clinic experienced the cardiac arrest more than once at the time of the extirpation of the abdominal tumor under hypothermia. This fact suggests that there are more important factors than bleeding as the cause of the cardiac arrest.

The 2nd case is a one year and 11 months old female having hepatoma. The great tumor weighing 785 g was removed with the subtotal resection of the right lobe of the liver. The blood loss was 1500 cc (Fig. 31). From several minutes before the end of the right subtotal hepatectomy, the pulsation of the carotid artery became feeble. Besides, as shown in Fig. 32, E. C. G.-ic findings showed a serious pattern. During operation, an adequate amount of blood was replaced by careful measurement of blood loss (Figs. 29 and 30). Nevertheless, why did the cardiac function decrease?

On the method of fluid and blood transfusion, we made an serious error in the above 2 cases by the following reason. In these 2 cases, as a routine method, the internal saphenous vein was canulated by cut-down for fluid and blood transfusion. An adequate amount of fluid and blood was replaced, observing the blood loss and urinary volume during dissection of the tumor under hypothermia. However, when the tumor was

**Fig. 32** Electrocardiogram during operation to Hepatoma (Lead II).  
(under Hypothermia) Subtotal Right Hepatectomy



dissected free so as to be movable, the central circulation is disturbed, because the tumor presses or strains the inferior vena cava by its removal or operative procedures. In the latter case, too, venous return to the heart is disturbed by the partial occlusion of the inferior vena cava or portal vein (right liver lobe being rotated). Therefore, blood which infused through the internal saphenous vein is pooled only in the peripheral site.

Thus, venous return to the heart is decreased and the decrease in coronary flow consequently might cause the cardiac arrest. In fact, E. C. G.-ic findings seen in the latter case show the course of the decrease in myocardial function. Fortunately, in the latter case, since it was suspected this mechanism of the cardiac arrest, rapid blood transfusion from the cubital vein was done. By doing so, E. C. G.-ic findings and blood pressure became normal. This fact shows that circulation was maintained normal by the sufficient venous return to the heart from the uninterrupted superior vena cava, and in these 2 cases blood transfusion through the internal saphenous vein was the inadequate procedure. Therefore, in the surgery for removal of a large abdominal tumor in children, the fluid and blood transfusion must be done through the cubital vein by cut-down.

In the application of hypothermia to the pediatric surgery, a dose of 0.1mg of neostigmine was injected subcutaneously several times with careful measurement of pulse rate at 27°C rectal temperature in order to prevent ventricular fibrillation. The child was cooled and rewarmed by the immersion method. Postoperative pulmonary edema was prevented by the 2 to 3 times subcutaneous injection of a dose of 0.5 mg per kg of promethazine after rewarming. To be noticed, no autonomic nerve blocking agents were administered as premedication.

Our experiences confirmed that even the profound or moderate hypothermia which has been known to be dangerous because of the occurrence of ventricular fibrillation or pulmonary edema could be safely employed clinically by the preoperative administration of E. F. A. and Vit. E., subcutaneous injection of neostigmine, infusion of an adequate



amount of blood and fluid, and the postoperative subcutaneous administration of promethazine.

Even if the cardiac arrest or ventricular fibrillation occurred, it will be easily converted to the normal cardiac beat as far as the above procedures were done. Our clinic employed the hypothermia at 23° to 28°C rectal temperature to the operation of the abdominal tumor in children so as not to repeat the above mentioned failure. Thereafter, except the above 2 cases, all were successfully operated without any complications.

To summarize, our new hypothermia ideals with the pediatric surgery as far as the above attentions were carefully taken. It is confirmed that even the poor risk patients seemed to die during or after operation in normothermia were successfully operated with the help of our new hypothermia. In children fluid and electrolytes must be carefully administered even postoperatively. If fluid intake by mouth is not to be expected, it is necessary to administer it through the intravenous drip infusion. It is stated that the daily water requirement in infants is about 100 cc per kg. However, the administration of water after operation must be restricted to 60 to 70 cc per kg daily because of influence of stress response. Besides, as the excretion of Na decreases for several days after operation, physiologic saline needs not to be administered within 2 days after operation. In children, 5% glucose solution must be infused, observing the water loss such as vaporization, urine, suction and vomiting. Usually, 5% glucose solution must be administered for four fifths of the water requirement and physiologic saline or RINGER's solution for one fifth.

### III. CONCLUSION

The experiences of clinical application of our new hypothermia to the intracranial operation and the pediatric surgery lead to the following results.

- 1) Preoperative administration of E. F. A. and Vit. E, subcutaneous injection of neostigmine during hypothermia and the subcutaneous administration of promethazine after rewarming were fully effective in the prevention of cardio-pulmonary complications. However, the preoperative administration of D. A. E. as used in hypothermia of dogs is not necessary.

- 2) Even the poor risk children such as the state of poor nutrition having large abdominal tumor were successfully operated under hypothermia.

- 3) The attention must be paid on the pre- and post- operative administration of fluid and electrolytes in pediatric surgery. Furthermore, blood and fluid replacement during operation must be done most carefully from the cubital vein with the drip infusion method in the case of extirpation of a large abdominal tumor.

- 4) The new technique of hypothermia proved to be useful in the intracranial surgery and pediatric surgery.

The author wishes to express his sincere gratitude to Dr. Y. HIKASA, the lecturer of our clinic, for his helpful suggestion and kind guidance in the course of the work. The author wishes to thank his collaborators Dr. H. SHIROTANI, Dr. T. KUYAMA, Dr. T. TOMIOKA, Dr. A. SAITO, Dr. T. OKUDA for their kind advice and help.

## REFERENCES

- 1) Adolph, E. F.: Responses to Hypothermia in Severe Species of Infant Mammals. *Am. J. Physiol.*, **166**, 75, 1951.
- 2) Araki, M. et al.: Experimental and Pathological Studies on Vitamin E Deficiency (Written in Japanese). *Vitamin*, **19**, 574, 1960.
- 3) Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gardon, R. A. and Greenwood, W. F.: Oxygen Transport and Utilization in Dogs at Low Temperature. *Am. J. Physiol.*, **160**, 125, 1950.
- 4) Deterling, R. A., Nelson, E., Bhonslay, S. and Howland, W.: Study of Basic Physiologic Changes Associated with Hypothermia. *Arch. Surg.*, **70**, 87, 1955.
- 5) Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A. and Bing, R. J.: Coronary Blood Flow and Myocardial Metabolism in Hypothermia. *Ann. Surg.*, **139**, 279, 1954.
- 6) Hanafusa, S.: Clinical Studies on the Nutritional Effects of Fat Emulsion Administered Intravenously and Usual Tube Feeding. *Arch. jap. Chirur.*, **28**, 1356, 1959.
- 7) Hayashi, Y. et al.: Study on Limit of Hypothermia-Especially on Cardiac Function (Written in Japanese). *J. jap. Anesthesiol.*, **6**, 59, 1957.
- 8) Hayashida, et al.: Study on Surgical Application of Hypothermia and Hypertension (Written in Japanese). *J. jap. Anesthesiol.*, **4**, 242, 1955.
- 9) Hegnauer, A. H., Shriber, W. J. and Haterius, H. D.: Cardiovascular Responses of the Dog to Immersion Hypothermia. *Am. J. Physiol.*, **161**, 455, 1950.
- 10) Hikasa, Y. et al.: Parenteral Administration of Fats. I. Fat Metabolism in Vivo, Studied with Fat Emulsion. *Arch. jap. Chirur.*, **27**, 736, 1958.
- 11) Hikasa, Y. et al.: Parenteral Administration of Fats. II. Clinical Application of Fat Emulsion. *Ibid.*, **27**, 736, 1958.
- 12) Hikasa, Y. et al.: Significance of Fat Nutrition. I. Surgical Diagnosis and Treatment, **1**, 332, 1959.
- 13) Hikasa, Y. et al.: Significance of Fat Nutrition. II. *Ibid.*, **2**, 117, 1960.
- 14) Hikasa, Y. et al.: Significance of Fat Nutrition. III. *Ibid.*, **2**, 253, 1960.
- 15) Hikasa, Y. et al.: Significance of Fat Nutrition. IV. *Ibid.*, **2**, 386, 1960.
- 16) Hikasa, Y. et al.: Significance of Fat Nutrition. V. *Ibid.*, **2**, 648, 1960.
- 17) Hikasa, Y. et al.: Significance of Fat Nutrition. VI. *Ibid.*, **2**, 931, 1960.
- 18) Kamimura, A.: Treatment of Frost Bite by Vitamin E (Written in Japanese). *J. New Remedies and Clinic*, **3**, 12, 1954.
- 19) Kamimura, A.: Prevention of Frost Bite by Vitamin E (Written in Japanese). *J. New Remedies and Clinic*, **4**, 114, 1955.
- 20) Kamimura, A.: Treatment of Dermatic Diseases by Vitamin E (Written in Japanese). *J. New Remedies and Clinic*, **5**, 363, 1956.
- 21) Kawahara, K.: Prevention and Therapeutic Effect of Thrombosis by Vitamin E (Written in Japanese). *Vitamin*, **14**, 924, 1958.
- 22) Kobayashi, M.: unpublished.
- 23) Kusunoki, T., Cbeng, H. C., McGuire, H. H. and Bosber, L. H.: Myocardial Dysfunction after Cardioplegia. *J. Thoracic and Cardiovascular Surg.*, **40**, 813, 1960.
- 24) McFarland, J. A., Thomas, L. B., Gilbert, J. W., and Horrow, A. G.: Myocardial Necrosis Following Elective Cardiac Arrest Induced with Potassium Citrate. *J. Thoracic and Cardiovascular Surg.*, **40**, 200, 1960.
- 25) Miyazaki, O.: Histochemical Study on Vitamin E (Written in Japanese). *Vitamin*, **19**, 279, 1960.
- 26) Montgomery, A. V., Prevedel, A. E. and Swan, H.: Prostigmin Inhibition of Ventricular Fibrillation in the Hypothermic Dog. *Circulation*, **10**, 721, 1954.
- 27) Moulder, P. V., Thompson, R. G., Smith, C. A., Siegel, B. L. and Adams, W. E.: Cardiac Surgery with Hypothermia and Acetylcholine Arrest. *J. Thoracic Surg.*, **32**, 360, 1956.
- 28) Nagase, M.: Experimental Study on Pathogenesis of Acute Postoperative Pulmonary Edema. *Arch. jap. Chirur.*, **29**, 67, 1960.
- 29) Oh, S.: The Influence of Vitamin E to the Experimental Arteriosclerosis (Written in Japanese). *Vitamin*, **17**, 365, 1959.
- 30) Ohmori, S. and Nakamura, Y.: Histological Study on Hypothermic Anesthesia (Written in Japanese).

- nese. J. jap. Anesthesiol., 6, 60, 1957.
- 31) Ohmori, S. and Nakamura, Y.: Investigation of Hypothermic Anesthesia from the Histological Point of View (Written in Japanese). J. jap. Anesthesiol., 6, 60, 1957.
  - 32) Onchi, Y. et al.: Experimental study on Histological Changes of Brain Caused by Hypoxia (Written in Japanese). J. jap. Anesthesiol., 6, 109, 1957.
  - 33) Penrod, K. E.: Cardiac Oxygenation During Severe Hypothermia in Dog. Am. J. Physiol., 114, 79, 1951.
  - 34) Virtue, R. W.: Hypothermic Anesthesia. Charles C. Thomas, Springfield, Illinois, 1955.
  - 35) Watanabe, A. et al.: Study on Electrocardiographic and Histological Findings of Brain after Circulatory Occlusion and Operation under Hypothermia and Hibernation (Written in Japanese). J. jap. Anesthesiol., 5, 87, 1956.
  - 36) Yamashita, Y.: Experimental Study of Vitamin E. Vitamin, 15, 330, 1958.
  - 37) Young, W. G., Sealy, W. C., Brown, I. W., Hewitt, W. C., Callaway, H. A., Merritt, D. H. and Harris, J. S.: A Method for Controlled Cardiac Arrest as an Adjunct to Open Heart Surgery. J. Thoracic Surg., 32, 604, 1956.

## 和 文 抄 録

# 超低体温麻酔法の基礎的並びに臨床的研究

京都大学医学部外科学教室第2講座（指導：青柳安誠教授）

桑 名 一 雄

最近に於ける心臓外科の進歩は、人工心肺と低体温麻酔法との発展によつてもたらされたと云つても過言ではない。併し、人工心肺は、常に大量のヘパリン血を必要とし、又脳及び冠状血管の空気栓塞の危険性もあり、又その装置の管理が極めて繁雑であるという欠点が存在する。それに反して低体温麻酔法では、生体を冷却して個体の新陳代謝を低下せしめて、心内手術操作を確実にを行うのに必要にして充分なる時間だけ血流を遮断し得る特性を有しているばかりでなく、人工心肺に較べてその経費も少くてすみ、又手術に際して完全なる Dry field が得られる点に於て優つてゐると云える。

一般に、血流遮断時間は体温の低下と共に延長する事が出来るが、従来より体温 $28^{\circ}\text{C}$ 以下になると、屢々心肺合併症が発生するとされて来た。その一つは心室細動であり、他は肺合併症である。そこでわれわれは、この中の肺合併症即ち肺水腫の予防対策について検討したのである。

一般に、低体温麻酔時には、毛細血管壁の透過性が異常に亢進し、循環血液は著しく濃縮して、末梢抵抗

は増大し、ひいては心臓に対して著しい負担を及ぼす結果となり、これが心室細動の発生をもたらすものと考えられて来たが、この心臓に対する負担は更に静脈圧の上昇をもたらし、肺水腫の原因になるものと考え、本研究に於ては、如何にすれば低体温麻酔時の毛細血管壁の透過性の異常亢進を防止し、又末梢血管の低温に対する抵抗性を強める事が出来るかについて検討した。

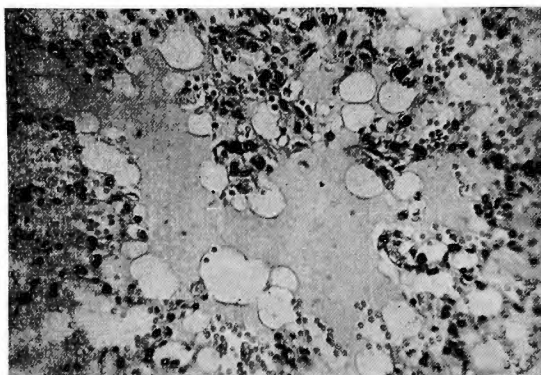
その結果、麻酔前に予め充分量の不可欠脂酸とビタミンEを投与し、術後 Prométhazine の皮下投与を行えば、たとい外界気温が $10^{\circ}\text{C}$ 以下という極寒期に於ても肺合併症を予防し得る許りでなく、術後2週間以上に亘り試獣を長期生存せしめる事が可能である事を明らかにする事が出来た。

そして更にわれわれの提唱する麻酔法によつて、直腸温 $22^{\circ}\text{C}$ 下に於て開胸し、20分及び50分間の血流遮断下に右心室切開を行い、次いでこれを縫合閉鎖し、閉胸して蘇生回復させた試獣について、実験直後から5日後、10日後、20日後、30日後と日時の経過を追つて、中枢神経系、肺臓、心臓、肝臓、腎臓、脾臓等の

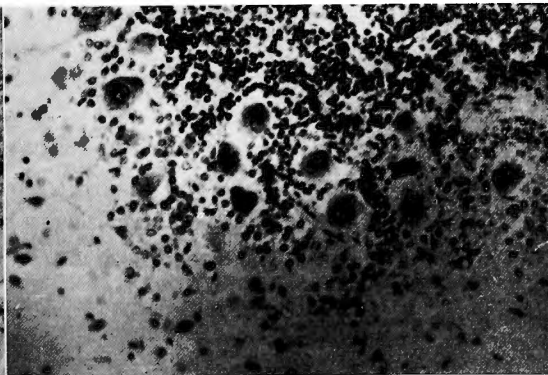
主要臓器についての組織学的検討を行い、22℃下では20分及び50分間の心血流遮断を行つても、これらの主要臓器に何らの危険性のない事を明らかにした。

次にわれわれは、この低体温麻酔法を、開頭術、体

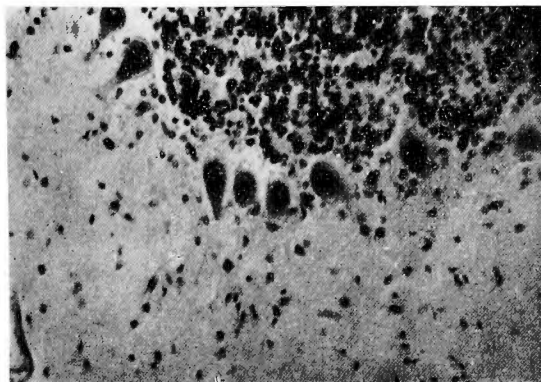
重9 kgという栄養不良の1才8ヵ月の幼児の Wilms' tumor及び1才11ヵ月の幼児の hepatoma の剔出手術に応用して吟味した結果、極めて優秀な低体温麻酔法である事を知つた。



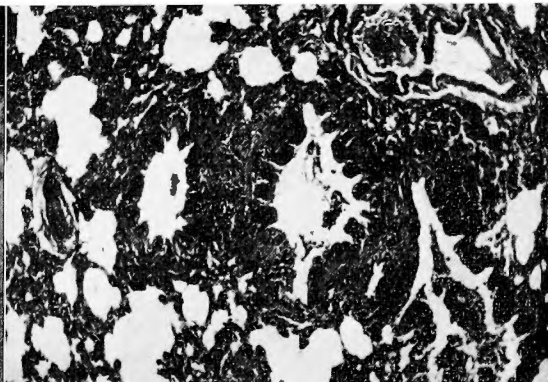
**Fig. 2** Lung. The dog who died of pulmonary edema.  $\times 400$



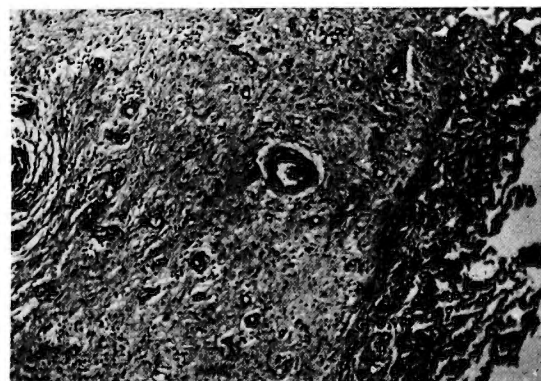
**Fig. 4** Purkinje's cells in cerebellum. 5 days after (Circulation was occluded for 20 minutes.)  $\times 400$



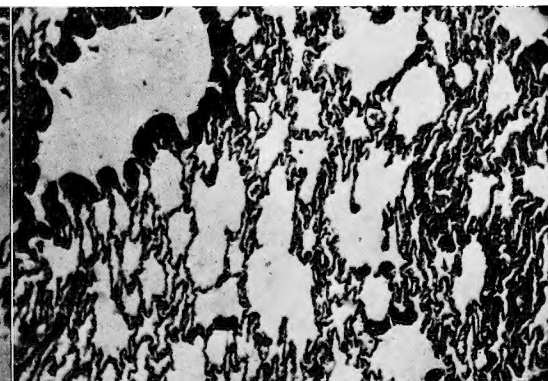
**Fig. 5** Purkinje's cells in cerebellum. 10 days after (Circulation was occluded for 50 minutes.)  $\times 400$



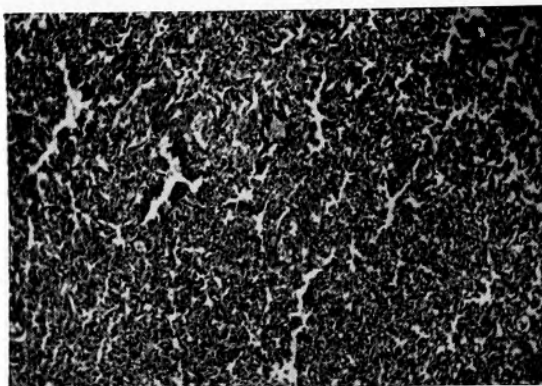
**Fig. 6** Lung. 5 days after (Circulation was occluded for 20 minutes.)  $\times 80$



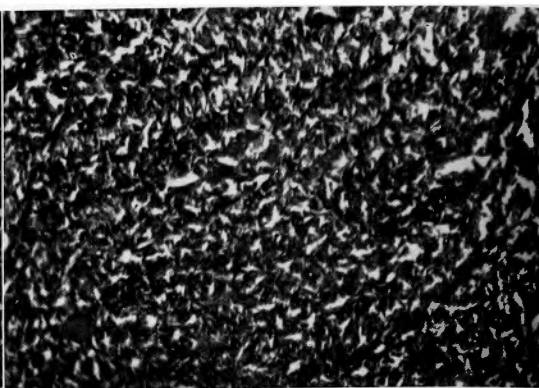
**Fig. 7** Granulation tissue and connective tissue of the pleura. 30 days after (Circulation was occluded for 20 minutes. The dog with myocardial insufficiency.)  $\times 80$



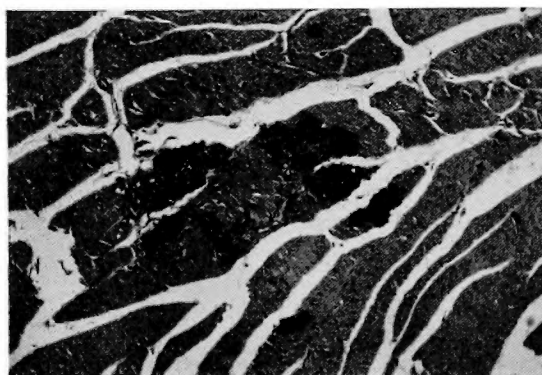
**Fig. 8** Lung. 20 days after (Circulation was occluded for 20 minutes.)  $\times 80$



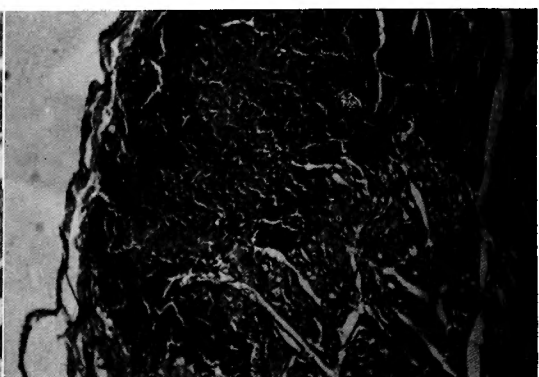
**Fig. 9** Lung. Immediately after (Circulation was occluded for 50 minutes.)  $\times 80$



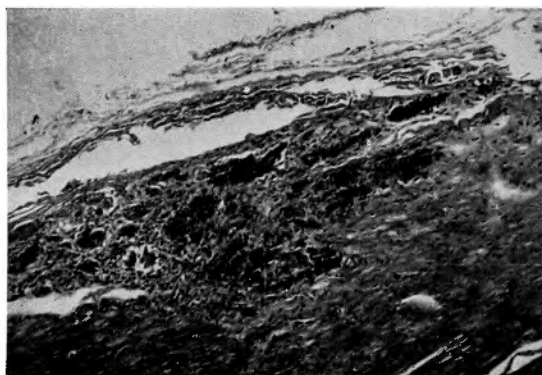
**Fig. 10** Heart. Immediately after (Circulation was occluded for 20 minutes.)  $\times 400$



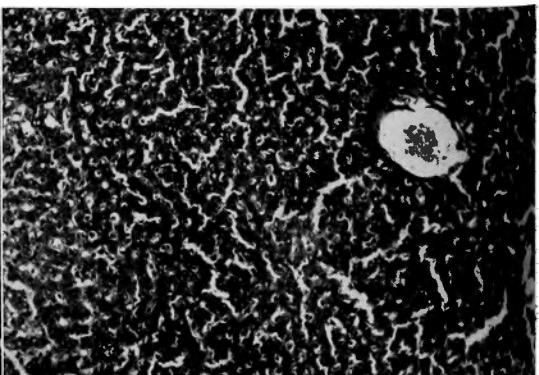
**Fig. 11** Heart. 30 days after (Circulation was occluded for 20 minutes.- The dog with myocardial insufficiency.)



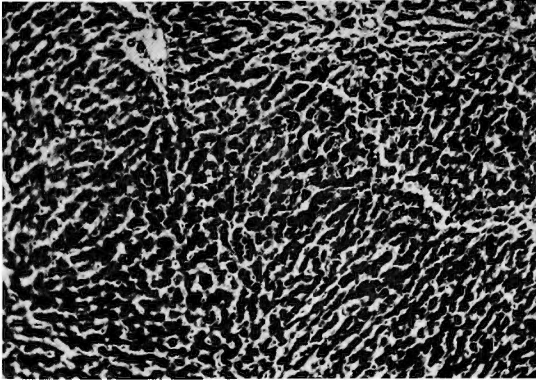
**Fig. 12** Heart. 5 days after (Circulation was occluded for 50 minutes.)  $\times 80$



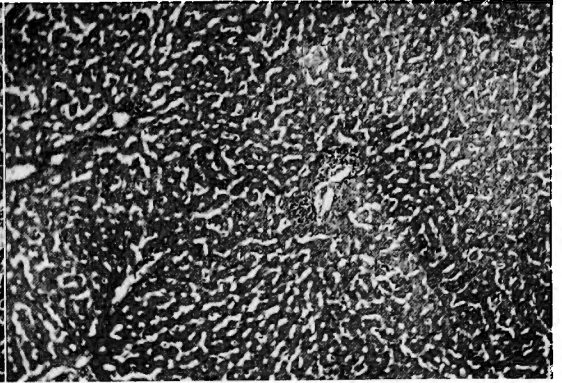
**Fig. 13** Heart. 30 days after (Circulation was occluded for 50 minutes.)  $\times 80$



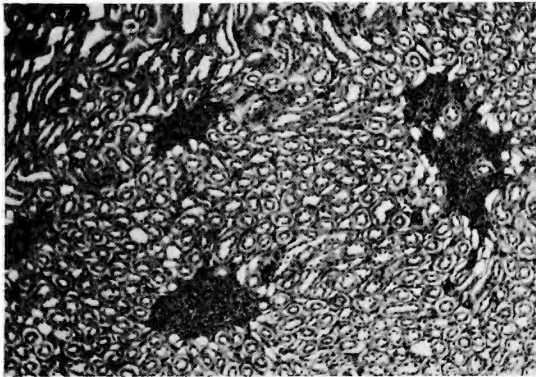
**Fig. 14** Liver. 5 days after (Circulation was occluded for 20 minutes.)  $\times 80$



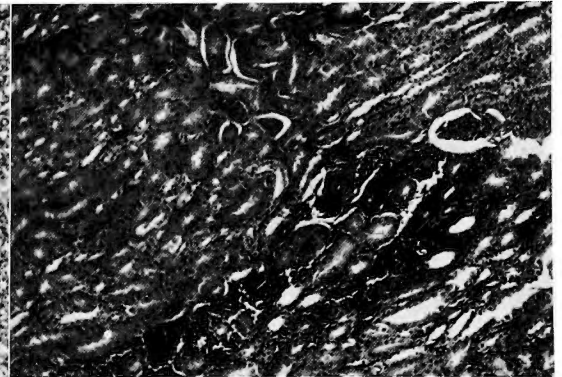
**Fig. 15** Liver. 5 days after (Circulation was occluded for 50 minutes.)  $\times 80$



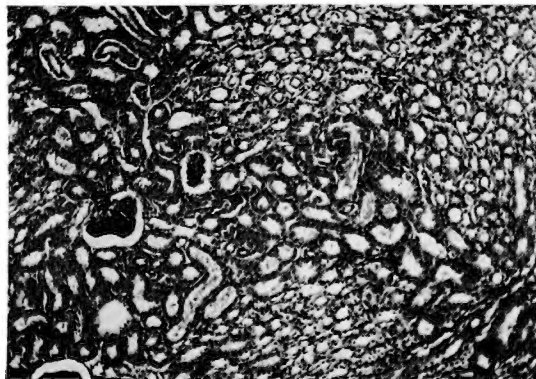
**Fig. 16** Liver. 20 days after (Circulation was occluded for 50 minutes.)  $\times 80$



**Fig. 17** Kidney. 30 days after (Circulation was occluded for 20 minutes.-The dog with myocardial insufficiency.) Medulla  $\times 80$



**Fig. 18** Kidney. 30 days after (Circulation was occluded for 20 minutes.- The dog with myocardial insufficiency.) Cortex  $\times 80$

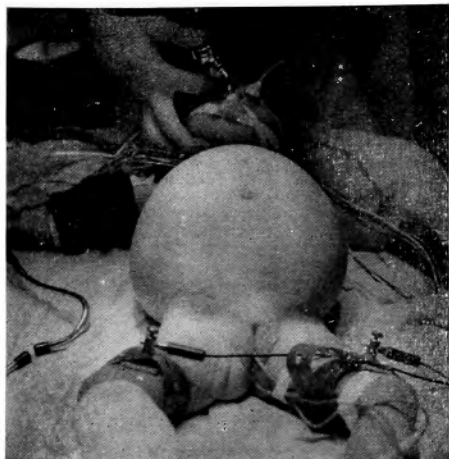


**Fig. 19** Kidney. 10 days after (Circulation was occluded for 50 minutes.)  $\times 80$

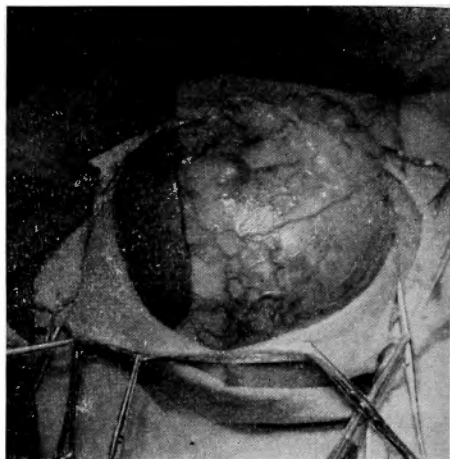


**Fig. 20** Spleen. Immediately after (Circulation was occluded for 20 minutes.)  $\times 80$

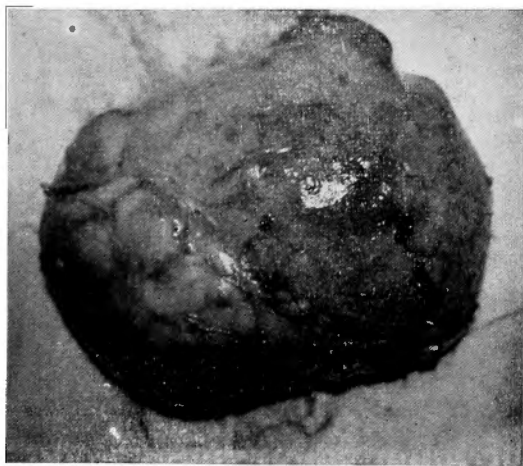




**Fig. 26** Photo. in the extirpation of Wilm's tumor. Before laparotomy



**Fig. 27** Photo. in the extirpation of Wilm's tumor. During laparotomy



**Fig. 28** Wilm's tumor (Weight 1.6 kg)



**Fig. 29** Photo. during operation to hepatoma  
During laparotomy-I



**←Fig. 30** Photo. during operation to hepatoma  
During laparotomy-II



**Fig. 31** Hepatoma (Weight 785 g)